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GRAVES DISEASE. ITS PATHOLOGY AND TREATMENT WITH CASES.

The subject of Graves disease is one ~~that~~ which has received the special attention of medical men and scientists very much of recent years, and although there has been a great advance in our knowledge of the pathological anatomy of this morbid condition, it has not as yet been followed by corresponding advance in successful treatment.

The condition was first fully described by Graves in 1835, and although there are records of earlier published cases: e.g. Flagani in 1802, an anonymous writer in 1816, Demours in 1818, Parry in 1825, Adelman in 1828, yet all the symptoms and their special character were not recognised until 1835.

In Germany the first detailed account of the condition was given by Basedow in 1840.

Besides the commoner nomenclature of Graves disease, exopthalmic goitre, and Basedow's disease,

other names have at various times been applied to the condition. e.g. Struma opthalmica, Cachexia opthalmica, cardio-thyroid exopthalmos.

In considering the aetiology: the greater frequency with which it occurs in women is marked. Most authorities putting it down to about 6 to I; among whom may be mentioned V.Graefe, Trousseau, Henock; Gowers[1] states the figure as high as 20 to I, Of 23 cases that I have had the opportunity of studying, 3 were males.

Graves disease may be met with at any time during life, but is most frequent between the ages of eighteen and forty-five: several cases have been reported as occurring in persons considerably over this limit: Gowers[1] mentions two cases at the ages of fifty-one and fifty-three; a case died at Guy's Hospital in 1868 at the age of fifty-eight. It may also occur in childhood; Fox[2] mentions a case at the age of twelve, a second was reported in the Lancet[3] at the age of ten and a half, and Dreshfeld[4] mentions two cases at the ages of twelve and three.

1. *Diseases of the Nervous System.*
2. *Lancet. vol. 1. 1894. p. 479.*
3. *Lancet. vol. 1. 1887. p. 1196.*
4. *Pract. Aug. 1896 p. 136.*

A hereditary tendency is not marked in Graves disease, although many cases have been recorded of it occurring in parents and children and in several members of the same family: I have met it occurring in the wife of a land-agent in Suffolk; two out of three daughters being also affected.

Not infrequently the ancestors antecedents of those suffering from Graves disease have been the subjects of epilepsy, insanity or other nervous disorder, but the condition is rare among the insane. In three out of twenty-three cases, I have traced a direct history of epilepsy, and in one case[1] where the patient died with acute mania, the brother died a short time previously in a status epilepticus.

The pathology of Graves disease opens up a wide field in which there is still a great diversity of opinion. Some authorities attributing the symptoms to a primary derangement of the nervous system, others to a toxic invasion, the nervous system being secondarily affected.

The commoner of the various theories advanced are that the symptoms are due to:—

[1] *Case I.*

1. Lesions leading to a paresis or paralysis of the cervical sympathetic.

2. Lesions leading to a paresis or paralysis of the sympathetic centres in the medulla.

3. Functional disturbance of the nervous elements in the medulla.

4. Changes causing a permanent stimulation of the sympathetic centres.

5. Passive Septic Invasion, in which the infective agency may act upon:

    a. The Thyroid gland, causing perversion of its function, the nervous system being secondarily affected.

    b. The Thyroid and Nervous system simultaneously.

    c. The Nervous system directly, the Thyroid gland being secondarily affected.

6. Auto-toxic infection from the Thyroid gland, the Nervous system being secondarily affected, due to its excessive or perverted secretion; not excluding a possible nervous causation for the primary changes in the gland.

1. That the symptoms of Graves disease are due to a lesion of the Cervical sympathetic causing paralysis of the vaso-motor nerves and consequent goitre with pulsation of the carotids and retinal vessels, along with an excited cardiac action by the permanent irritation of the excito-motor nerves of the heart — which also run in the sympathetic — is unlikely: as two of the symptoms are accounted for by paralysis, and the third by stimulation. Further, it is very improbable that paralysis of the vaso-motor nerves would produce goitre and exopthalmos; experimental division in animals having failed to do so. Nor does exopthalmic goitre follow paralysis of the sympathetic in man, although the pupillary symptoms due to the same may be well marked. And again, the changes in the Thyroid are not such as would be produced by mere vascular engorgement even if such a condition were present.

2. That the symptoms are due to lesions leading to paresis or paralysis of the vaso-motor centres in the brain, receives support from the oft-quoted experiment of Filehne and Bienfait.

Filehne's[1] opinion was that Graves disease might be

[1] Societé Médicale des Hôpitaux. Feb 23rd 1894.

produced by paralysis of certain nerve regions controlled by the medulla oblongata, and that the points traversed in common by the nerve paths contained, are the restiform bodies. The exopthalmos and goitre he attributed to the dilation of the blood-vessels; and the cardiac symptoms to want of tone in the vagus. In his experiments section of the anterior fourth of the restiform bodies was followed by exopthalmos, in some experiments by exopthalmos and goitre, and in one experiment tachycardia was also produced..

Bienfait[1] also made bilateral transverse sections through the grey matter of the restiform bodies in rabbits with marked alteration in cardiac rhythm, and fine regular tremors; in one-third of the experiments exopthalmos was also produced, and in one-fourth distinct hyperæmia of the Thyroid gland.

In support of this theory is a most interesting case quoted by Mannheim[2] in which the symptoms of Graves disease developed in a few days after the occurrence of bulbar haemorrhage and improved with absorption of the clot. The various complications also point to a central lesion, e.g. paralysis of the associated movements of the eye, glycosuria etc.

1. *Bulletin de l'Acad. Royale de Médecine de Belgique. 1890.*
2. *Der Morbus Gravesii. Berlin. 1894.*

But the results of post-mortem examinations have not shown lesions to exist of such a nature as to cause these paralytic symptoms.

8. Many authorities in our country contend that Graves disease is due to a functional disturbance of the central nerve elements.

Hutchinson[1] attributes the symptoms to specific changes in the tissue metabolism, probably due to functional alteration in the central nervous system; and explains the benefit derived from Thyroidectomy by the removal of a secretion that accelerates tissue metabolism.

Gowers[2] designates the malady as a neurosis. He accounts for the tachycardia by Marey's physiological law, that there is an inverse ratio between the frequency of the pulse and the general blood pressure; so that a lowered arterial tone and a frequently acting heart coincide, in consequence of their relationship to a central mechanism. He attributes all the symptoms to a central derangement of the sympathetic, and taking the above relationship between pulse-rate and pressure, together with the negative results of

1 Lancet. vol. II. 1896 p 896.
2. Diseases of the Nervous System.

post-mortem examinations, and the character of the disturbances, he considers that the morbid state is one of function, and that the centre which determines this relationship between the pulse-rate and pressure is in the medulla.

Oliver[1] however states that an increased pulse-rate is not coincident with a lowered blood pressure.

Those who contend that Graves disease is a neurosis bring forward in support the fact that it so frequently follows emotional disturbance: that is, that it may be started by a derangement of the cortex.
It is very unlikely that emotion can cause Graves disease; the condition probably existing already in a minor degree and the nerve influence merely exaggerating the symptoms.

4. The view that the symptoms are due to a permanent stimulation of the sympathetic centres has many supporters, especially in France.

Abadie[2] contends that there is permanent stimulation of that portion of the cervical sympathetic which presides over the dilation of the vessels of the orbit, thyroid gland and over the heart. The thyroid

1. Pulse Gauzing.
2. Arch. d'Opth. Paris. Nov. 1896
Clinique Opth. Paris. 1896. p. 132.

enlargement he considers a secondary effect of this distention; he admits that superabundance of the thyroid secretion may be injurious. His view is that the lesion is nuclear; the nuclei of the nerves influencing the heart and blood-vessels indicated, being situated in the bulb and upper part of the cord; whilst those influencing the limb and trunk vessels are situated lower down and therefore escape. The nuclei placed in the bulb being affected singly or in groups. He suggests, as has been suggested by others before, that in the cases which derived benefit from thyroidectomy, the good result has been due to free division of the sympathetic.

In support of this theory may be advanced the facts that:-

The Exopthalmos may be enormous whilst the other systems are extremely slight.

The occurrence of Unilateral cases.

The fact that the vessels in the head and neck are distended and pulsate, whilst the arteries of the other parts are in a normal state.

Even if the above discriminating lesions do exist in Graves disease, it is very doubtful whether a mere

increased vascularity would lead to the changes in the Thyroid gland as described by Victor Horsley, Greenfield and others.

5. That Graves disease is due to a toxic agency has supporters, especially amongst continental writers. Carle and Lustig hold that it may be due to a passive septic invasion, and pointed out its infective character in 1890,[1] supported later by Grube;[2] also Dr Hector Mackenzie[3] has pointed out that suppuration seems to predispose to Graves disease.

In support of septic invasion are the numerous cases recorded of exopthalmic goitre having disappeared after removal of nasal disease.[4] Hopman[5] records a case in which treatment directed to chronic atrophy of the nasal mucous membrane led to recovery.
Grainger-Stewart and Gibson[6] record a case of marked improvement following treatment of a hypertrophied condition of the naso-pharyngeal mucous membrane.

Treatment of a diseased condition of the Inferior turbinate bones has also been followed by improvement. Hack[7] removed the inferior turbinate bones which were the seat of thickening in a case of Graves disease.

1. Giornale di R. Academia di Med. di Torino - Aug. 1890
2. Neurol. Centralbe. No 5. 1894.
3. Lancet. Sep. 13. 1890.
4. Burnett - Diseases of the Nose & the Accessory Cavities.
5. Berlin. Klin. Woch. XXV. 42. 1888.
6. Edinb. Hosp. Report. vol. I.
7. Deutsche med. Woch. XII. 25. 1886.

from childhood, with recovery.

Amelioration of the symptoms after galvano-cauterization of the inferior turbinate bones is reported by Frankël,[1] Bobone[2] and Spencer Watson.[3]

Spicer and Stokes[4] recorded cases of nasal polypus concomitant with Graves disease, the symptoms improving on treatment of the nasal condition.

Mackenzie[5] states that patients often complain of a stuffed-up feeling in the nose.

In support of the septic invasion theory is also advanced the fact that the symptoms are aggravated by quinsies, which are comparatively common in individuals suffering from Graves disease.
Riviere[6] and others have reported cases.

Blake[7] considers the condition to be due to a passive septic invasion to which the toxic agency of the Thyroid secretion is added causing a neuritis of the medulla, pons and cervical sympathetic.

1. Berlin. Klin. Woch. XXV. iii. 1888.
2. Annales d'Oculist. XCVI 260. 1888.
3. Med. Soc. Trans. vol. XV p 309.
4. Lancet. vol. II. 1894. p 1158.
5. Lancet. vol. II. 1890. p. 545.
6. La glande Thyroide et les Goitres. (Baillere. Paris 1893.
7. Myxoedema, Cretinism and the Goitres. ps 41-46.

The infective influence of Influenza has also been supported. Dreschfeld[1] records forty cases, five following epidemic influenza, and one case in which the symptoms were much increased by an attack of influenza.

The Infective Theory has also been advanced as explaining the sudden development, or the marked increase of the symptoms following emotion.

Roger[2], discussing the pathology of shock, has proved that there is an arrest of metabolism, as shewn by a diminution of carbonic acid gas in the venous blood. Those holding this infective theory attribute the symptoms following emotion as due to the toxic influence of the results of arrested katabolism.

Against the theory of a passive septic invasion is the fact that enlargement of the lymphatic glands is not one of the symptoms met with in Graves disease, as it would probably be if this theory were correct. In twenty-three cases, I have met enlargement of the cervical glands in two only; and in the forty carefully recorded cases of Dreschfeld there was glandular enlargement in one only. Further, if Graves disease were due to Septic invasion, this morbid condition

1. Practitioner. Aug. 1896. p. 170.
2. Archives de Physiology. Nov 1893.

would occur even oftener than it does, and would be one of the common sequelae of continued suppurations.

6. Last for consideration is the theory that Graves disease is due to auto-toxic infection from the excessive or perverted Thyroid gland secretion, causing secondary changes in the nervous system.

This view is supported in our country by Victor Horsley, Greenfield, Murray, Byrom Bramwell and others, but meets most support on the continent, especially amongst German writers.

Greenfield[1] considers the condition to be a primary affection of the Thyroid gland, with an excessive and probably perverted secretion leading to secondary changes - irritative and degenerative in nature - in the cervical sympathetic ganglia, in the ganglionic centres in the mid-brain, and in the commencement of the cranial nerves.

Victor Horsley[2] also considers the abnormal condition of the Thyroid gland as the primary cause of the symptoms. The Thyroid secretion being perverted. Both these authorities do not exclude a possible nervous causation for the state of the gland and its altered secretary condition.

1. Lancet. vol. II 1893. p. 1555.
2. British Med. Journal. Vol II. 1896. p 1623.

Before attempting to arrive at a conclusion as to the probable pathology of Graves disease, it will be necessary to consider the facts gained from recorded post-mortem examinations.

Many cases have at various times been published with seemingly varied and negative results.

Greenfield[1], in five recorded cases, found in all of them wide-spread, sub-acute, inflammatory and degenerative changes, but most marked in the cervical sympathetic ganglia and in the ganglionic centres in the medulla.

Of the various negative results doubtless many of the earlier records are due to an unreliable microscopic examination. And of the numerous seemingly varied results, many seem traceable to an inflammatory origin, the haemorrhages and softenings described being probably due to subsequent degenerative changes.

Cheadle[2] mentions the brain and spinal cord as having a perfectly normal appearance to the naked eye, microscopic examination revealing great dilation of the vessels of the medulla and of the cervical region of the cord.

Mackenzie[3] describes softening of the corpora

1. Lancet. vol II. 1893. p 1155.
2. St. Georges' Hosp. Reports - vol IX p. 803. 1878.
3. Trans. Clin. Soc. of London. vol I. p. 15. 1868.

quadrigemina and medulla oblongata, especially on their posterior aspect. Hale White[1] describes haemorrhage into the Aqueduct of Sylvius and poster part of the bulb as far as the Restiform bodies. Grainger-Stewart and Gibson[2], a haemorrhage on the floor of the fourth ventricle; further, that the haemorrhage was of recent date, whereas the exopthalmic goitre had existed for some time. The haemorrhage probably being due to minute structural changes in the blood-vessel. Giegel speaks of proliferation of neuroglia with turgescence of vessels. Dr Reith[3] described the cervical ganglia as in a state which might be due to an inflammatory condition having occurred. Dr Hughes[4] described the cervical ganglia as infiltrated with round cells.

Of the changes in the Thyroid — which strangely, seem only to have been recorded in recent literature — very definite and similar records are given by Greenfield[5], Victor Horsley[6], Murray[7], Grainger-Stewart and Gibson[8].

1. British Med. Journal. vol. I. p. 699 1889.
2. Edin. Hosp. Reports. vol II p. 291.
3. Medical Times. p 581. 1685.
4. Dublin Medical Journal. p. 540. 1884.
5. Lancet. Vol. I. 1893. p 1495.
6. Brit. Med. Journal. vol. II. 1896. p. 1623.
7. Lancet. vol. II 1896. p. 895.
8. Edin. Hosp. Rep. Vol. I. p. 215.

These essentially consist in:-

Alteration in the character of the Epithelium, the normal cubical epithelium of the acini becoming columnar.

Alteration in the outline of the acini, which instead of being more or less rounded show a conglomeration of newly-formed tubules, lined by a single layer of cubical epithelial cells; which in many cases encroaching from the sides, completely obliterate the acini. All the changes resembling a glandular structure undergoing active evolution.

Alteration in the secretion. The semi-transparent colloid material usually present in the acini being replaced by granular debris (due probably as pointed out by Greenfield to the desquamation of the epithelium consequent on the catarrhal condition present in the gland) and occasionally by a thin watery fluid.

The important points for consideration before advancing a theory as to the probable pathology of Exopthalmic goitre are:-

I. The existence of Unilateral cases, and the fact that with decrease in size of the Thyroid gland you

may have decrease of the exopthalmos on the same side.[1]

2. The condition of the Thyroid gland; a state of hyperplasia which could not be due to mere vascular engorgement even if such existed, but Greenfield[2] has shewn that there is no vascular engorgement, merely an increase of blood vessels such as might be accounted for by the active evolution the gland has undergone. Grainger Stewart and Gibson[3] reporting the minute changes in the Thyroid, also states that there was no marked engorgement.

These two facts alone, to which others of the earlier symptoms might be added-e.g.polyuria and glycosuria - make it probable that the primary changes are in the central nervous system. As soon as the Thyroid gland comes under the influence of a deranged innervation, the changes as described in the gland ensue, the toxic influence of the deranged secretion causing wide-spread central changes, especially affecting those centres whose functional activity has already been altered. The centres most affected being the ganglionic centres in the medulla and the symptoms of Graves disease being due to a permanent stimulation of these centres.

1. *Vide Case IV.*
2. *Lancet. vol II. 1893 p 1555.*
3. *Edin. Hosp. Rep. vol I. p. 215.*

That the Thyroid secretion aggravates and may cause many of the symptoms is supported by the following facts.

1. When the secreting area of the abnormal gland is diminished either by Thyroidectomy or by fibrosis, produced artificially or otherwise, there is a subsequent diminution in the symptoms, and often a cure.

2. That the wide-spread central changes already mentioned would best be accounted for by the influence of a toxic agency circulating in the blood, and also the various complications such as Cramp, Hyperæsthesia, altered knee-jerks, and localised œdema, by a peripheral neuritis due to the same cause.

3. The striking similarity between the symptoms of Thyroidism and Graves disease.

4. The contrast between Graves disease and Myxœdema.

That Thyroidectomy has a beneficial effect is undoubted; removal of part of the gland being followed by good results and atrophy of the remainder.
Recent statistics on the subject published by Starr[1]

1. Med. News. April 18. 1896.

shew that in 190 cases, 28 died immediately after the operation, 74 were reported as cured, forty-five as improved, and 8 as not improved.

Murray[1] records a case in which a fibrosis produced by the injection of iodine resulted in a cure.

Ord[2] mentioned a case in which, due to too rapid diminution in the size of the thyroid gland by treatment, symptoms of Myxoedema followed on those of exopthalmic goitre.

Greenfield[3] has shewn that the proliferation in the thyroid gland is liable to be followed by fibrous overgrowth, and the functional inactivity occurring in consequence leads to Myxoedema.

This fibrosis is the probable explanation of the spontaneous cure of Graves disease; and the fact that Myxoedema does not invariably follow Graves disease is only explicable by the large degree of involutionary changes that may occur in our bodies without leaving serious results.

Comparing the symptoms produced by Thyroidism and the symptoms of Graves disease, a remarkable case is recorded by Béclère.[4]

1. Lancet. vol. II 1896. p. 875.
2. At a meeting of the Lond. Med. Soc. Oct 21. 1893.
3. Lancet. vol. II p. 1496. (1896)
4. La Semaine Médicale. 1894. p 462.

A woman aged thirty-one, suffering from myxoedema, took by mistake 92 grammes of the Thyroid gland in eleven days; with the result that she suffered from:- tachycardia, exopthalmos, brilliancy of the eye, transient tremors of the arm, rise in temperature, insomnia, polyuria, glycosuria, albuminuria and partial paraplegia.

Without producing poisonous symptoms, the therapeutic action of the Thyroid gland resembles many of the symptoms of Graves disease; there is an increase in pulse-rate, respiration and temperature, in the action of the skin, in the amount of urine and urea passed, and a general loss of vascular tone.

Small doses of the normal gland when administered cause an immediate but temporary increase in the pulse-rate and rate of respiration; with an accumulation of the active principle in the system, the immediate increase is less marked but the general rate of pulse and respiration is raised.

The above facts have been gained by careful observation of the action of the Thyroid gland during treatment for various morbid conditions, and when taken by myself during health.

The following case shews very typically the action of the drug:-

Richard G. machinist, aged eighteen, complained of a constant feeling of drowsiness; he had a heavy expression. A somewhat uncertain diagnosis of commencing myxœdema was given. The patient's condition was watched for one week, and then 15 grammes of the Thyroid extract per day were administered in the form of tabellæ. A carefully measured ordinary diet and 46 ounces of fluid per diem were given, before, during and after the Thyroid treatment.

The following figures record the changes in his pulse-rate, respiration and temperature and in the amount of urine and urea passed.

	Average morning pulse.	Average evening pulse.	Average rate of resp. M.	Average rate of resp. E.	Average Temp. M.	Average Temp. E.	Amount of urine in ounces.	Amount of urea in grammes.
1st week. No treatment.	72	73	22	23	97·7°	98·2°	24	20
2nd week. 15 grs. Thyroid ext. per diem.	73	75	24	26	97·8°	97·9°	31	27
3rd week. " " "	84	86	25	25	97·9°	98·3°	35	31
4th week " " "	94	98	24	26	98·1°	98·4°	42	47
5th week. No treatment.	87	89	24	26	97·5	98	32	29
6th week. " "	76	80	22	24	97·2	97·6	×	×

During one week of the treatment the pulse-rate and rate of respiration were taken at each administration of a five grain tabella of the Thyroid extract, and also for the two subsequent hours.

The following figures shew the variations which occurred.

		Thyroid.				Thyroid.				Thyroid.			Amount of Urine per diem.	Amount of Urea per diem.
Date.		a.m. 10.	a.m. 11.	12.	p.m. 1.	p.m. 2.	p.m. 3.	p.m. 4.	p.m. 5.	p.m. 6.	p.m. 7.	p.m. 8.		
Nov. 26.	Pulse	80.	100	84									22	16 grammes
	Respiration	26	28	26										
" 27.	Pulse	82.	106.	88.		82	104	88		78	100	80	42	39 grammes
	Respiration	26	28	26		24	28	26		24	26	24		
" 28.	Pulse.	94	100	90									23	23 grammes
	Respiration	26	28	26										
" 29.	Pulse.	88	100	96									46	44 grammes
	Respiration	26	28	26										
" 30.	Pulse.	94	100	90		90	100	100		90	96	86	25	21 grammes
	Respiration	26	28	26		24	28	28		24	26	24		
Dec. 1	Pulse	88	96	92		88	98	88		88	94	88	41	36 grammes
	Respiration	22	24	24		26	28	24		22	24	22		
" 2.	Pulse	92	94	90		102	110	92		86	92	80	45	42 grammes
	Respiration	22	24	22		26	28	24		22	24	20		

The contrast afforded by the symptoms of Graves disease and Myxoedema as pointed out by Byrom Bramwell[1] are very marked, and Greenfield[2] has further drawn attention to the fact that post-mortem changes occurring in the nervous system in Graves disease and Myxoedema are very similar in their localization, but that the former are of a sub-acute inflammatory nature, the latter more in the nature of a fibrosis.

Turning our attention to the secretion of the Thyroid gland in this morbid condition, there seems to be some difference of opinion as to the amount of colloid material present in the abnormal state of the gland.
Greenfield[3] states that there is an enormous increase in the secreting tubules of the Thyroid and also of the colloid material in the spaces of the gland.
Martius[4] again, states that the colloid material found in the Thyroid is usually diminished and always chemically abnormal. Murray[5] also holds that there is a diminished amount of colloid material, probably because of its more rapid removal.
Victor Horsley[6] states that the original colloid matter entirely disappears, being replaced by a granular debris, and occasionally by a thin watery fluid, and

1. Edinb. Med. Journ. May 1893.
2. Lancet vol II 1893. p. 1553.
3. Edinb Med Journ. May 1893.
4. Berliner Klinik May 1896.
5. Lancet. vol. II 1896. p. 895.
6. British Med. Journ. vol II. 1896. p1623.

Hutchinson[1] also supports this diminution in the colloid material.

The concensus of opinion therefore seems to point to the fact that the colloid material is diminished in Graves disease.

Hutchinson[2] pointed out in 1896 that the colloid matter was alone the active principle in Thyroid secretion. More recently he has separated from the gland a nucleo-albumin, the pure colloid material, and the extractives (creatinin, xanthin etc.) He has shewn that the extractives have no power in exerting the specific action of the Thyroid, nor yet the nucleo-albumin, which he considers is probably derived from the cells lining the acini; and that the pure colloid material is the only active constituent in the gland. Further, this colloid material can be split up into a proteid and a non-proteid part, the colloid material owing its activity mainly to the non-proteid part.

Gourlay[3] has pointed out that the nucleo-albumin present in the normal thyroid is particularly rich in phosphorus, and certainly has the power of producing intravascular coagulation.

1. Lancet. vol. II 1896. p. 897.
2. British Med. Journ. Vol. 1. 1897. p. 194.
   Journal of Physiology. vol. XX. p. 474.
3. Journal of Physiology March 22. 1894.

Since the pure colloid matter is alone the active constituent of Thyroid secretion, the symptoms of Graves disease or their exaggeration, if due to Thyroid secretion, must be due to this colloid matter. But the Colloid matter being diminished in the normal state of the gland; it is only reasonable to suppose that it must be perverted in its character in order to compensate for its diminution in quantity; there being no proof that it is more rapidly absorbed, as suggested by Murray.

On the other hand the nucleo-albumin must in the abnormal gland be in great excess, if secreted by the cells lining the acini as suggested by Hutchinson, due to the greatly increased secreting area. Gourlay has shewn this nucleo-albumin to be rich in phosphorus and having the power to produce intravascular coagulation. The symptoms of Graves disease might therefore be due to the excess of this nucleo-albumin.

Considering the symptoms of the disease in so far as they have a bearing on the probable pathology, the impairment of the consensual movement of the upper lid in association with the eyeball, known as Von Groefe's sign is interesting. This symptom has

been attributed to paresis of the orbicularis and the recti,[1] also to paresis of the Temporal division of the Tempero-Facial nerve.[2] That the phenomenon is due to paresis of the orbicularis is highly improbable, as the symptom occurs in a movement in which the orbicularis takes no part, and is absent when the orbicularis contracts so as to close the eye.

If cocaine be applied to the conjunctiva there is a retraction and defective descent similar to V.Groefe's sign, the cocaine probably acting as an irritant on the sympathetic nerves, for Jessop[3] found this effect was not produced when the cocaine was applied some days after division of the sympathetic.

This points to the fact that the symptom is due to over-action of the sympathetic.

The muscular tremor which is such a frequent symptom points to a Thyroidal connection; for as Victor Horsley[4] has pointed out, the tremor in all forms of Thyroidal lesions is exactly similar to the tremor of acute cachexia strumipriva in thyroidectomised animals.

The coexistence of Graves disease with Acromegaly, as pointed out by Murray, is also interesting.

1. Blake. Brain. vol. XV. p. 121.
2. Maude. Before Lond. Med. Soc. Oct. 16. 1893.
3. Trans. Opth. Soc. vol V p. 240. Vol. VI. p. 123.
4. Brit. Med. Journ. vol. II. 1896. p. 1624.

1.

Five cases have been recorded. Glycosuria being also present in four of the cases and Phthisis in two. Acromegaly is probably due in some way to changes in the Petuitary gland. If the theory of internal secretion be correct, Acromegaly and Graves disease are both probably due to an excessive or altered secretion in the petuitary and thyroid glands respectively. The coexistence of these two morbid states suggests some common cause as bringing about similar changes in the Petuitary and Thyroid glands, probably central because of the coexistence of glycosuria.

1. Murray. Edinb. Med. Journ. Vol. I no 2. p. 170. 1897.
Lancereaux. Semaine Méd. p. 61. 1895.
Henrot. Semaine Méd. p 61. 1895.
Valat. Brit: Med. Journ. Oct 3. 1896.

TREATMENT.

The abnormal state of the Thyroid gland in Graves disease seems clearly to indicate that any line of treatment which is adopted should include special measures for its improvement.

With regard to surgical treatment, the various operations which have from time to time been attempted are:-

Removal of part or the whole of the Thyroid gland.

Ligature of the Thyroidal arteries.

Nerve stretching.

Removal or cauterization of the Inferior Turbinate bones.

Electrolysis of the Thyroid.

Injection of the Thyroid to produce fibrosis.

Thyroidectomy requires consideration. Recent statistics[1] leave it beyond doubt that many cases are cured or alleviated by this operation, but the mortality is at present as high as 12 per cent; and as in many cases the symptoms are only alleviated, and there is also the tendency to spontaneous cure, Thyroidectomy cannot at present be considered as altogether satisfactory.

1. Starr- Med. News. April 18. 1896.

The results of electrolysis of the Thyroid have not been satisfactory, but cases have been reported as cured after the injection of iodine[1], and It seems a very reasonable treatment to promote a moderate fibrosis in the gland by this means; yet there is always the risk of producing a too extensive fibrosis with the result that myxodœma would supervene. Reference to surgical treatment directed to the Inferior Turbinate bones has already been made.

Local treatment that has been tried consists mainly in the application of cold and electricity. I have on several occasions tried ice to the Thyroid but without any beneficial effects.
Cold to the præcordia, as ice bags or Leiters coils undoubtedly does good. The pulse-rate by this means may be greatly diminished; but even if this is not marked, the patient has relief from the more distressing symptoms due to the tachycardia and dyspnœa.
Cold may be applied for half-an-hour night and morning, and the time gradually increased until the ice bags or coils can be worn for several hours daily.
To obtain any lasting results from cold to the præcordia the treatment must continue over several

[1] Lancet. vol. II. 1896. p. 875

months. It is also important to examine the urine periodically for albumen.

Electricity, as a weak galvanic current to the Thyroid daily, has been reported as giving good results[1] and the Faradic current has also been recommended.[2]

Turning our attention to general treatment; rest and tranquility of mind are important factors. In one case of a woman aged twenty-seven, the only treatment for several weeks was the recumbent posture, except for half-an-hour in the evening; and a light diet, at first mainly milk. The pulse which at first averaged 120 per minute dropped to an average of 86. The Thyroid enlargement remained the same but the exopthalmos was undoubtedly improved.

Medical treatment has up to the present been found to be very uncertain. Iron, arsenic, strychnine, quinine and other tonics have given very varied results. Iron which seems to be indicated when anæmia is marked, occasionally seems to be actually harmful; and the same may be said of the drug in acute cases.

As to the beneficial effects of Iodides and Iodine very contradictory statements exist.

1. Dreschfeld. Pract: Aug. 1896. p. 153.
2. Vigouroux & Charcot - Bart: Hosp. Rep. 1892. p. 25.

Recently at St Thomas' Hospital several cases of Graves disease have been treated with Iodised Salt, the patients taking equal parts of Iodide of Potassium and common salt with their meals; two cases certainly became quite well and others shewed some improvement. Drugs that slow the pulse seem indicated, but the results obtained from the use of such drugs as Digitalis, Strophanthus etc. have been very variable. Best results have been recorded from the use of Belladonna, and I have found this drug most useful, given in gradually increasing doses. This drug certainly seems the most rational medical treatment, considering the active state of the Thyroid gland.

Treatment by Thyroid extract, which is now quite abandoned, in all acute cases greatly augments the symptoms. In chronic cases temporary benefit may be derived from Thyroid feeding, probably because fibroid changes have occurred in the gland.

Dietary is most important, milk being considered by some in the light of a specific. Cod-Liver Oil, Maltine etc. I have found most useful.

In recent years the theory of an internal secretion from glandular structures has been advanced. Landa's[1] experiments have shewn that there may be an oppositeness between two vascular organs. He shewed that in extirpation of the Thyroid and Spleen no myxoedema followed, as is the case when only the Thyroid is extirpated.

M. Kaufmann has established by experiment the fact that the internal secretion of the Pancreas has an inhibitory influence on the formation of sugar in the Liver.

Victor Horsley[2] has pointed out that there is strong evidence that the Thyroid gland is a secretary gland, as shewn by King, Barber and others, and that the secretion passes along the lymphatics into the general circulation and so is distributed all over the body. It is possible therefore that the secretion of the Thymus may exert an inhibitory or counteracting influence on the secretion of the Thyroid.

Post-mortem examinations in Graves disease have not usually revealed the Thymus gland to be hypertrophied, but there are several reported cases in which it has been.[3]

1. Centrabl f. inn. Med. No 12. 1894.
2. Brit. Med. Journ. Jan. 30th 1892.
3. Hamilton. Lancet. vol 2. 1895. p. 896.
   Murray. Brit. Med. Journ. Feb. 6. 1896.

In Germany many cases of Graves disease have been reported as cured and benefited by Thymus feeding. Cunningham[1.] records three cases of recovery and marked improvement. Owen[2.] was the first to draw attention to the benefit derived from Thymus feeding in our country. I have tried preparations of the Thymus gland in four cases: two shewed decided improvement, one, no improvement at all, and the fourth commenced to improve, but unfortunately I was unable to follow up the case.
I was induced to try Thymus treatment by a peculiar accident.

Althea W. aged twenty-one, was admitted to the East Suffolk Hospital to be treated for obesity. Thyroid extract in tabellae were administered, until at the end of the third week, when she was taking 15 grs per diem, her pulse rate averaged 88 in the morning, 94 in the evening.
Quite suddenly the pulse-rate dropped 10 per minute, and on more careful examination of the pulse I found the following to be the various pulse rates, although the tabellae were continued.

1. Med. Record. June 15. 1895.
2. Brit. Med. Journ. Vol. I. 1895. p 361.

Tabellae Thyroid extract

Tabellae Thymus extract

Date	a.m. 8	a.m 9	a.m 10		p.m. 6	p.m. 7	p.m. 8
Dec. 22nd	80.	80	72	Pulse.	84	72	72
	22	20	22	Respiration.	22	20	22
Dec 23rd	76	76	72	Pulse.	84	80	72
	20	20	20	Respiration.	20	20	20
Dec. 24th	78	76	72	Pulse.	84	80	72
	20	20	20	Respiration.	20	20	20

On making enquiries I found that the tabellae of Thyroid extract had run short, and that the dispenser had sent up tabellae of Thymus extract, being similar in appearence; with the result that in two days the morning and evening pulse-rates were 80 and 84 per minute instead of 88 and 94; the pulse on admission being 76 and 80. The patient had for three weeks taken Thyroid extract, and as the pulse usually continues without much change for several days after the Thyroid treatment is stopped, the sudden drop in the pulse-rate must have been due to the Thymus extract counter-acting the Thyroid extract.

There is no doubt that Thymus feeding in cases of Graves disease improves the vascular tone[1], and it may be to this that the general improvement is due.

[1] *Vide Case II.*

Another gland extract that is reported to be beneficial is the extract from the Suprarenals. Suprarenal treatment gives benefit in all conditions in which there is a loss of vaso-motor tone.[1] Still more recently Ballet and Enriquez have used the blood serum of dogs, in which the Thyroid has been extirpated.

[1] Oliver. Brit. Med. Journ. vol. II. 1895. p. 655.

CASES OF GRAVES DISEASE.

CASE NO I.

Frances Emily W. aet 37 single. Engaged in household duties. Admitted as an In-patient to the East Suffolk Hospital on February 20th 1895.

Complaining of her sight failing in the left eye, also of great thirst and of passing an increased amount of urine.

The sight has been failing for eleven months, and the thirst and passing of an increased amount of urine has been noticed for three months.

Her father and mother are both alive, aged respectively 86 and 79. She has had three brothers, two of whom are at present alive and in good health; the third brother suffered from epilepsy all his life and died during an epileptic fit at the age of 35.
She has also one sister who is strong and healthy.

Her home surroundings are exceptionally good and clean. She has led an abstemious life and has always had a small appetite until lately, when her appetite has increased.

The patient has had measles and scarlet fever in childhood; four years ago she had a very severe attack of Influenza, and since then she has never been very strong. Her mental faculties were affected and she became excitable and irritable, constantly complaining of pain at the back of her head and neck. Her failing sight has been a source of great anxiety to her and continued to be so during the course of her subsequent illness. A month previous to admission she went to Moorfields Hospital; there she was informed that she was suffering from cataract, but that ,as she was also suffering from diabetes, no operation could be performed.

The patient is well nourished and of good colour. Her expression is staring and she is of a decidedly neurotic temperament. The temperature is normal. The tongue is red and raw. Appetite large, and she complains of thirst,acidity and discomfort after food. The bowels act three or four times every day. There is no enlargemnet of the Thyroid or other glands. The circulatory and respiratory systems present no abnormality. The pulse-rate averaging 80 per minute. No palpitation or dyspnoea. The colour in her face

is high and she very rapidly flushes.

The urine passed varies from 70 to 80 ounces per day, sp. gr. 1020. no albumen. no sugar.

The catamenia are regular.

There is a slight degree of exopthalmus in both eyes. with some catarrhal conjunctivitis. Mature cataract in the left eye, and commencing cataract in the right eye. On looking downwards the descent of the upper lid is of a jerky and spasmodic nature, but the sclerotic does not shew above the cornea.

The deep and superficial reflexes are unaltered.

The intelligence is below the average, and the patient is of an excitable and hysterical nature and suffers from insomnia.

The family history was obtained at a visit to the patient's home, and the relatives presented a strikingly strong and healthy appearence.

As treatment, Potassium Bromide, Belladonna, Citrate of Quinine and Iron were administered, with Bromidia, when required at night; and a light nourishing diet.

Soon after admission she complained of a tugging sensation over the Thyroid gland, but no enlargement could be felt. A weak galvanic current was applied

to the neck twice a day.
The urine was daily examined but no sugar was found.

After being in the Hospital one month she was discharged on March 20th I895.
When she left there were no signs of circulatory disturbance; her condition being very much the same as when she came in one month previously.
The Polyuria varied greatly, sometimes the amount of urine passed being sub-normal, and at other times as much as I00 ounces per day.

Soon after her discharge she paid a second visit to the Royal Opthalmic Hospital at Moorfields but was refused operative treatment.

On January IIth I896 she again came under my notice at the Out-patient department of the East Suffolk Hospital, nine months after her discharge as an in-patient from the same institution.

She now complained of indigestion, severe bilious attacks and occasional diarrhoea.
The symptoms of Graves disease were now all well marked. The exopthalmos was greatly increased and the Thyroid was enlarged, especially the right lobe—
The Thyroid enlargement had been noticed by the patient two or three months previously.

The pulse-rate could not be relied on as it varied so greatly from visit to visit, but rarely exceded I00 per minute. The cardiac dulness was normal.

She also presented herself at the Opthalmic department and was anxious to have an operation for cataract performed.

On April I5 I896 she was re-admitted as an in-patient, fourteen months after she first came under my notice.

She was now much thinner, anaemic and with all the symptoms of Graves disease well marked; except that the circulatory system did not seem affected in proportion to the other systems.

Although only 38 years of age, the patient looked at least 50.

The temperature was normal. The tongue red and raw. The appetite was large and she suffered greatly from thirst. All the signs of gastro-intestinal irritation were well marked; the patient occasionally vomiting small quantities of very acid bile stained fluid, diarrhoea was constant, the bowels acting four or five times every day. Both the stomach and liver dulness were increased. The liver extending to the third inter-

interspace above,and the lower border could be distinctly felt in the abdomen.

The Thyroid gland was very much enlarged; the right lobe being more so than the left.

The spleen came just short of the mid-axillary line.

The cervical lymphatic glands could be distinctly felt.

Examination of the blood shewed there to be 2,800,000 red blood corpuscles per cubic ~~centi~~ millimetre, and the hoemoglobin reduced to 45 per cent.

There was no palpitation of dyspnoea except on exertion, but the patient frequently felt very faint.

The Apex beat was felt in the fifth interspace and the right and left borders of the heart were respectively two and three-and-a-half inches from the mid-sternal line.

A soft systolic murmur was heard all over the precordia not intensified at the Mitral or Tricusped areas but rather more audible at the base of the heart.

This murmur was also heard over the Thyroid gland and the vessels of the neck.

The pulse rate was about 100 per minute,regular,small and of low tension.

The Respiratory system shewed nothing abnormal.
The skin was moist and clammy,her face was pale with a hectic patch on each cheek, but she readily flushed and perspired under excitement.
The hair all over the body was very scanty and her finger nails had a blueish unhealthy appearence.
The urinary system shewed no abnormality. The patient was now passing about 50 ounces per day.
The catamenia had been absent for nine months.

Exopthalmos was present in a most marked degree, and there was great widening of both palpebral apertures. On looking down,delay in the descent of the upper lid was marked. The patient was nearly blind from double cataract, and there was a diffuse congestion of the ocular conjunctiva in both eyes.
The reflexes were normal. A constant muscular tremor was present, occasionally the movements becoming almost choreaic,especially if the patient was watched.

Her intelligence was decidedly defective, the patient at times becoming very excitable, and at other times extremely morose; and she would indulge in fits of uncontrollable weeping. Insomnia was most marked.

On admission she was confined to bed,given a light

nourishing diet, and especial attention was paid to the gastro-intestinal disturbances, and to the congested condition of her conjunctiva and cornea. After the gastro-intestinal condition had somewhat improved she was given Thyroid Extract tabloids (Burroughs and Wellcome) three times a day. There was a decided reaction with this drug and the temperature which up to the present had been sub-normal went up to 100° F. and both pulse and respiration became more rapid; her general condition becoming worse, the Thyroid treatment was stopped.

Arsenic, Belladonna, Potassium Bromide were tried but without any benefit.

May 10th. The pulse though not so rapid as when patient was admitted was less regular.

May 14th. For the previous week the patient suffered from excessive diarrhoea which had been continuous since her admission. Opiates afforded little relief to this symptom, and the best results were obtained from 20 minims of Aromatic Sulphuric acid given three times a day. The temperature during this time was abnormally low, running for

days together as low as 96° to 97°.

May 20th. The patient had a sharp attack of Follicular Tonsilitis. She was treated with Potassium Chlorate and iron. During the attack of Tonsilitis the diarrhoea was very troublesome.

June 7th. The general condition continued about the same, but the pulse since the attack of tonsilitis had become more rapid. The patient suffered less from diarrhoea.

June 17th. As the patient had repeatedly requested that something should be done for her sight, it was decided to risk the operation for extraction, with the hope that it might relieve her mental condition.

The left eye was operated upon. The lens which was hypermature was delivered spontaneously; considering the amount of exophthalmos that was present the wound did well, although the operation was followed by extreme yellowish chemosis of the ocular conjunctiva, which continued for a fortnight and then subsided. The vision steadily improved.

July 5th. The patient's condition had improved, she was more cheerful and the exopthalmos seemed to be less, and she was allowed to go about the ward. She was at this time taking Citrate of Iron and Quinine, Sodium Bromide and Ammonia.

July 20th. The improvement continued, the patient was on ordinary diet, and was going out into the garden. It was decided to discharge her towards the end of the month. The pulse-rate was high, about 100 per minute.

July 26th. The patient did not seem quite so well. During the day her manner was most peculiar and the widening of the palpebral aperture was very apparent. In the evening the exopthalmos seemed suddenly to become much worse, the pulse became very rapid, 130 to 140 per minute, irregular and thin, and she developed a most excitable state of mind with delusions. It was impossible to procure sleep during the night although strong hypnotics were administered; and next morning she was a raving maniac; tearing her clothes and hair and refusing all food.

The exopthalmos became so great that dislocation of the eye-balls seemed inevitable. The heart was too rapid to count, and the patient was bathed in perspiration.

July 28th. The patient's condition continued the same, she was given nutrient enemata and took a little food.

July 30th. She was removed to the Borough Asylum, where she was placed in a padded room and was fed with a stomach pump. Six days after her removal she died.

This case which I had the opportunity of studying during the greater part of its course, presents several points of interest. The history of epilepsy in the family, a severe illness after which the mental faculties were affected. The existence of early polyuria which did not continue as the disease advanced. The presence of cataracts, the nature of which must remain a doubtful point; possibly they were diabetic in origin, but from Feb. 20th 1895 to July 30th 1896 though her urine was carefully tested at regular intervals no sugar was ever found. It is possible that the cataracts were due to trophic changes, the

the lens being an epidermic structure, and might be affected similarly to the other epidermic structures, e.g. hair and nails.

The constancy of the gastro-intestinal disturbance and the abnormally low temperature were a marked feature. The improvement following on the cataract extraction was very noticeable, and also the rapidity with which the exopthalmos and heart symptoms increased immediately prior to, and during the course of the acute mania.

The attack of Follicular tonsilitis supports Dr Hector Mackenzie's statement as to its frequency in Graves disease, Follicular tonsilitis occurring in nine out of forty cases recorded by him.[1]

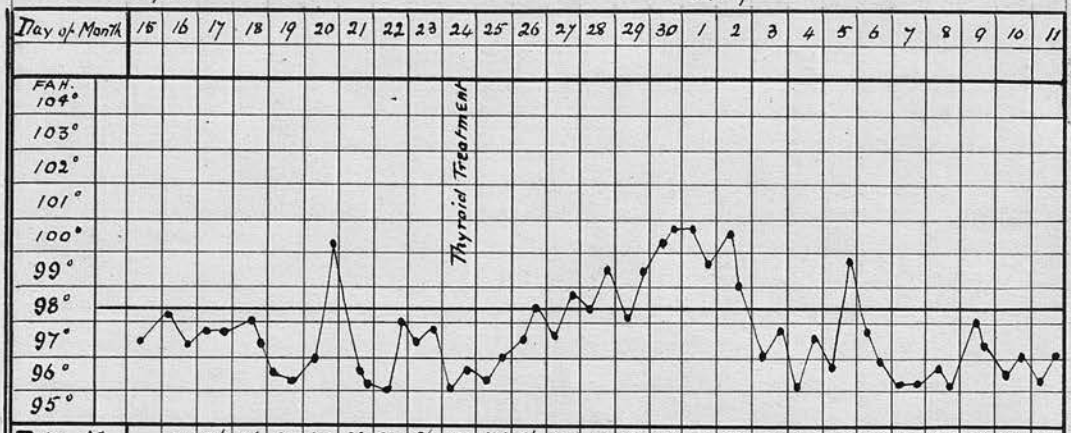
A post-mortem examination was made at the Borough Asylum; nothing abnormal being found in the nervous system; but as no microscopic examination was made, the results may be considered valueless.

I was unfortunately unable to attend.

[1] Lancet - Sep. 13. 1890.

Frances Emily W. aet. 38. Graves disease resulting in death with acute mania.

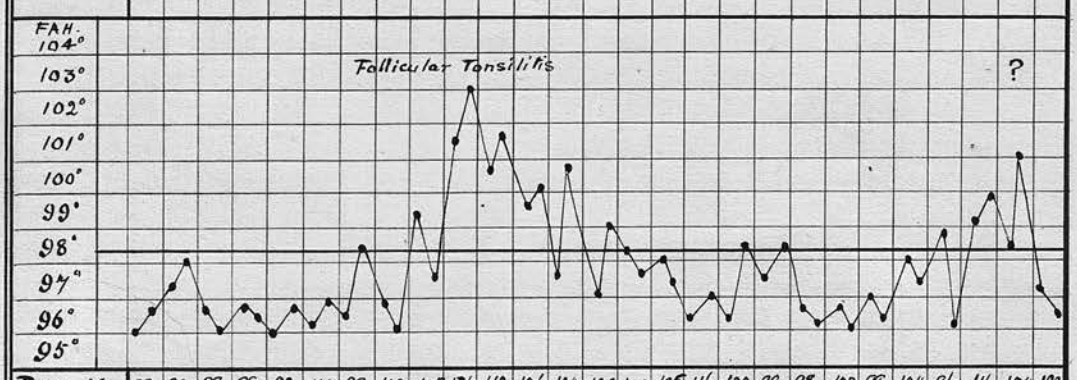
April — May



Day of Month	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	1	2	3	4	5	6	7	8	9	10	11
Pulse M.		102	96	96	92	100	92	88	96	100	100	96	104	108	110	106	120	105	100	104	94	88	90	96	86	88	90
Pulse E.	120	110	100	96	110	102	98	100	110	105	98	98	110	122	120	130	126	120	124	100	98	96	90	100	90	86	90
Resp. M.		26	24	24	26	24	24	24	24	28	24	22	24	24	26	28	28	24	24	24	26	22	22	26	24	24	24
Resp. E.	28	28	28	26	28	24	26	26	28	30	24	26	28	26	32	30	28	24	26	26	28	24	26	26	28	26	28
Stools.	3	5	3	4	4	6	2	1	3	0	1	3	5	5	2	4	6	5	7	4	5	1	3	1	4	7	7
Quantity			43	53	37	60	53	49	63	·	·	·	52	61	29	·	·	·	·	46	57	49	·	·	·	·	68
Sp. Gr.			1020	1020	1024	1017	1020	1020	1020	·	·	·	1022	1020	1024	·	·	·	·	1026	·	·	·	·	·	·	1015
Albumen			0	0	0	0	0	0	0	·	·	·	0	0	0	·	·	·	·	0	·	·	·	·	·	·	0
Sugar.			0	0	0	0	0	0	0	·	·	·	0	0	0	·	·	·	·	0	·	·	·	·	·	·	0

Urine

May — June



Day of Month	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	1	2	3	4	5	6	7
Pulse M.	98	90	88	88	92	100	98	100	105	136	110	106	104	120	100	106	116	100	98	98	100	98	104	96	116	104	100
Pulse E.	100	98	90	96	100	104	110	120	126	136	140	120	120	110	108	120	120	120	100	110	100	104	116	100	120	126	100
Resp. M.	26	24	24	26	26	26	24	28	24	30	32	28	26	28	26	26	28	24	26	26	24	26	24	24	28	24	26
Resp. E.	28	26	26	28	26	28	26	28	32	34	30	28	28	30	28	32	28	28	28	26	28	26	28	26	28	28	28
Stools	6	7	2	1	2	3	3	3	3	11	9	7	7	9	2	6	3	1	3	1	2	3	3	3	0	0	2
Quantity	58	·	·	·	·	·	56	48	62	·	·	·	·	42	·	·	·	·	·	·	54	·	·	·	·	·	·
Sp. Gr.	·	·	·	·	·	·	1024	·	·	·	·	·	·	1022	·	·	·	·	·	·	1020	·	·	·	·	·	·
Albumen	·	·	·	·	·	·	0	·	·	·	·	·	·	0	·	·	·	·	·	·	0	·	·	·	·	·	·
Sugar.	·	·	·	·	·	·	0	·	·	·	·	·	·	0	·	·	·	·	·	·	0	·	·	·	·	·	·

Urine

June — July

Day of Month	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	1	2	3	4
										Catheterization																	
Pulse M.	98	96	96	100	104	96	90	88	92	100	120	106	100	96	98	96	100	100	98	102	98	90	96	92	90	98	86
Pulse E.	106	98	100	102	116	100	100	100	106	116	120	120	110	100	98	98	98	112	98	96	116	108	96	100	98	98	90
Resp. M.	26	24	24	26	24	24	26	26	22	24	28	24	24	24	22	26	22	24	22	26	24	22	26	24	20	24	22
Resp E.	26	26	24	28	28	28	28	28	26	28	28	26	26	24	24	24	24	28	26	26	28	26	24	26	26	24	24
Stools.	2	7	5	0	7	5	6	7	3	5	3	4	4	6	2	1	3	0	1	3	4	2	2	1	3	0	2
urine. Quantity	.	.	.	.	.	.	50	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Sp. gr.	.	.	.	.	.	.	1025	.	.	.	.	.	.	1020	.	.	.	.	.	.	1020	.	.	.	.	.	.
Albumen.	.	.	.	.	.	.	0	.	.	.	.	.	.	0	.	.	.	.	.	.	0	.	.	.	.	.	.
Sugar.	.	.	.	.	.	.	0	.	.	.	.	.	.	0	.	.	.	.	.	.	0	.	.	.	.	.	.

July

Day of Month	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31.
Pulse M.	88	90	88	80	100	90					88	98	100	98	102	90	90					136	148	160	.	.	
Pulse E.	100	96	90	96	100	98					100	98	116	100	116	104	96					130	.	.	.	.	
Resp. M.	22	24	22	24	24	24					24	22	26	24	24	24	24					.	.	.	.	.	
Resp. E.	26	26	26	24	28	26					24	24	28	24	26	28	26					.	.	.	.	.	
Stools	5	2	1	3	2	4					2	1	3	.	.	2	4										
urine Quantity	.	.	.	.	.	.					.	.	.	.	.	.	.										
Sp. gr.	1024	.	.	.	.	.					.	1024	.	.	.	.	.										
Albumen	0	.	.	.	.	.					.	0	.	.	.	.	.										
Sugar.	0	.	.	.	.	.					.	0	.	.	.	.	.										

CASE NO II

Hannah S. aet. 26. Domestic servant, unmarried. Admitted to East Suffolk Hospital Dec. 29th 1896. January Ist 1897.

The father is alive and well, aged 64. her mother died three months ago, for two years previous to her death she suffered from paraplegia. Two brothers and four sisters are alive. The mother was an extremely excitable woman and two of the sisters are nervous and hysterical.

The patient has never had any illness, except measles when a child.

The home surroundings are healthy.

Six years ago the patient first noticed prominence of the eyes, more marked in the right; this was followed by a swelling in the neck. About two years ago she first suffered from palpitation, which rapidly became troublesome after its commencement.

I had seen the patient prior to this date when an in-patient at the East Suffolk Hospital from July 17th to Oct. 15th 1895.

She at that time complained of palpitation which had commenced three months previously. Exopthalmos was present in both eyes, there was a uniform enlargement

of the Thyroid gland, and the muscular tremor was well marked. The pulse-rate was about I20 and she suffered from palpitation. Sickness was a marked feature in her illness at that time, and she suffered from recurring attacks of diarrhoea. The urine was acid, specific gravity I025, with traces of albumen.

She improved under treatment, which was mainly directed to the alleviation of the gastro-intestinal disturbance. But a few weeks prior to her discharge her condition became worse, her pulse-rate going up to I30 or I40, with persistent diarrhoea and sickness. She left the hospital, contrary to advice, to give evidence in a family law-suit.

In November I895 she went to Guy's Hospital, where she was treated as an in-patient. When there, her pulse was very rapid,and cold was applied to the præcordia in the form of ice-bags. She remained at Guy's Hospital two months; when discharged the palpitation was much less troublesome, but the gastro-intestinal symptoms continued.

In March I896 she nearly died from exhaustion following uncontrollable diarrhoea.
The pulse-rate became very rapid subsequently, and the benefit derived from her treatment at Guy's

Hospital did not continue.

During the ensuing year she was treated by my friend Dr Edwardes-Ker, every conceivable treatment being tried. In December she consented to again come to the East Suffolk Hospital in order to enable me to try Thymus treatment.

On admission she weighed 7st. 3 lbs, muscular development was poor. She was pale and had a nervous staring expression and was of a decidedly nervous temperament. The temperature ranged from 97.5° to 100° F The lips were dry, the teeth decayed and very friable, the tongue was raw, the appetite, which used to be somewhat capicious, was now increased; there was not excessive thirst. Sickness was not at this time troublesome, and diarrhoea though present was not excessive.

There was no enlargement of the cervical or other lymphatic glands. Both lobes of the Thyroid were enlarged, but especially the right one, the circumference round the neck being 13 1/2 inches.
On placing the hand over the Thyroid gland, marked palpitation was felt; but if various points were examined over the enlarged gland, pulsation was really only present where the Thyroid gland over-lapped

the vessels in the neck, and in the region of the Thyroid arteries.

The Thyroidal enlargement was more marked than when the patient was in the Hospital in 1895.

An examination of the blood shewed 2,800,000 red blood-corpuscles per cubic ~~centi~~ milli metre, and the hoemoglobin reduced to 40 per cent.

Palpitation and dyspnoea were present, greatly aggravated by excitement or exertion.

The Apex beat was in the fifth interspace. The right border of the heart 2+1/2 inches and the left border 3+1/2 inches from the mid-sternal line. A somewhat impure first sound could be heard at the apex, and in the tricuspid area a soft systolic murmur, continued up the sternum; the second sound was unaltered.

A distinct systolic murmur was present over the vessels in the neck and over the Thyroid gland, and a continuous venous hum over the Jugular veins.

The pulse was irregular, small and of very variable tension and from 100 to 130 per minute.

The loss in the vascular tone, as shewn by Oliver's Arteriometer is shewn by the following reversed radial measurements.

Radial Diameter in Millimetres.

	Sitting.	Recumbent.
January 2nd 1897.	1·3	1·6
" "	1·2	1·7
January 3rd 1897.	1·4	1·7

The respiration was very rapid, 26 to 30 per minute. but otherwise no abnormal phenomena were observed in the respiratory system.

The skin was moist, perspiration occasionally very profuse, urticaria factitia was well marked.
The hair, of which the patient used to have a large quantity, was very scanty and during the last year had become grey. There was no oedema.
The urine was acid, sp.gr. 1025, traces of albumen, no sugar, copious urates, the daily amount being about 30 ounces.
The catamenia had been absent for two years.
The pupils were normal, exopthalmos was present in both eyes, but especially in the right, the retraction of the upper lid in the right eye being very marked.
On looking down there was a delay of descent in both eyelids, more marked in the right. The exopthalmos was greater than when in the Hospital in 1895.

Superficial reflexes were absent and the deep reflexes were diminished, and sensation was impaired in the lower extremities.

A fine regular muscular tremor was present, especially noticeable in the fore arm; the patient was also very restless, constantly moving her arms, legs and body. even during sleep.

The vaso-motor functions were very much deranged, a tâche cerebrale being very well marked, the pulp of the finger drawn lightly across the chest causing a broad vivid line; perspiration was also free.

The patient was nervous, but intelligent; she did not sleep well.

On admission the patient was confined to bed, she was given a light nourishing diet consisting of milk, chicken, fish and a small quantity of meat.

For the first week there was no medical treatment.

January 6th. The patient was given three drachms of the Elixir of Thymus gland (prepared by Messrs. Allen and Hanbury) per diem.

A drachm of the Elixir corresponding to 5 grains of the Thymus extract.

The dose was gradually increased until

on February 7th the patient was taking an ounce and a half of the elixir during the day.

January 20th. The general condition had decidedly improved. The exopthalmos was better. The Thyroid was the same size; but the most marked improvement was in the vaso-motor functions, the tâche cerebrale had entirely disappeared and the patient was no longer troubled with perspiration; the action of the bowels was less frequent.

January 23rd. The catamenia were present for the first time in two years, being about normal in quantity, and continuing for four days.

February 3rd. The general improvement continued, the temperature also becoming more regular. There was still no marked alteration in the size of the Thyroid although it seemed softer.

February IIth. Thymus treatment was stopped and then re-commenced in a day or two. Six drachms of the Elixir per diem were given, which ~~were~~ dose was

continued until her discharge.

February 28rd. The catamenia were again present. The patient now weighed eight stone, having increased eleven pounds since her admission.

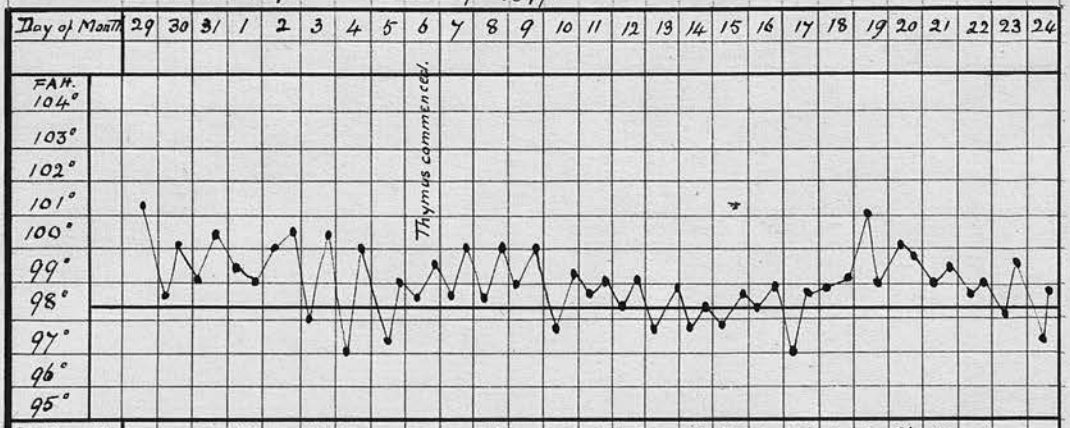
March 20th. The patient's general condition had continued to improve. The exopthalmos in the left eye had almost disappeared but was still distinct in the right eye. The Thyroid was three-quarters of an inch less in diameter. The patient was now going about the wards for two hours every afternoon, and her pulse had fallen to 70 per minute; the normal vaso-motor tone, estimated by Oliver's arteriometer, had been restored.

April 10th. The patient was discharged. Prior to this she had been helping in the wards. There was marked improvement in every respect, except in the size of the Thyroid which had not varied much. She weighed eight stone, six pounds, having gained seventeen pounds during treatment.

The pulse-rate varied from 60 to 80 per minute. The reflexes were still diminished, and the sensibility of the lower extremities was slightly impaired.

Hannah S. aet. 26. Graves Disease.
Thymus treatment.

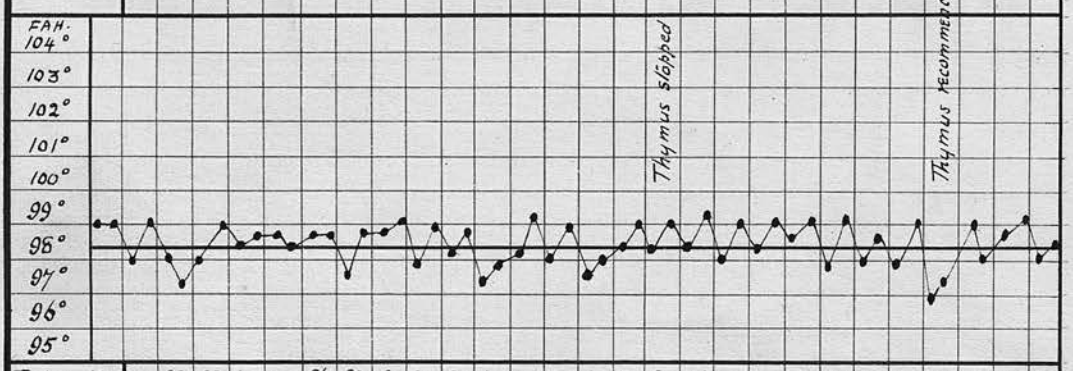
December. 1896. January. 1897.



Day of Month	29	30	31	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Pulse M.		100	114	120	104	110	104	104	90	104	96	110	120	120	120	100	96	98	90	96	90	90	86	100	106	108	100
Pulse E.	136	110	120	126	110	110	120	104	110	120	120	130	136	120	110	160	100	100	100	98	108	100	90	104	106	110	108
Resp. M.		24	26	30	28	32	36	30	25	28	30	28	28	30	26	33	26	26	24	24	24	24	24	26	28	24	24
Resp. E.	34	28	32	28	30	30	36	30	28	36	30	30	28	30	30	30	28	28	26	26	28	26	24	28	28	26	26
Stools	1	4	4	5	4	2	6	4	2	1	5	1	3	1	2	3	0	2	1	1	1	4	5	4	2	1	0
Quantity	·	·	·	36	28	31	40	30	32	26	28	36	26	18	36	42	40	26	31	24	26	37	30	28	26	26	33
Sp. Gr.	·	·	·	1026	1026	1020	·	·	·	·	·	·	1026	·	·	·	·	·	·	1025	·	·	·	·	·	·	·
Albumen	·	·	·	X	X	X	X	·	·	·	·	·	X	·	·	·	·	·	·	?	X	X	·	·	·	?	·
Sugar	·	·	·	0	0	0	0	·	·	·	·	·	0	·	·	·	·	·	·	0	·	·	·	·	·	·	·
Weight.									7st. 3lbs.							7st. 5lbs.							7st. 7lbs				

urine.

January. February.



Day of Month	25	26	27	28	29	30	31	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Pulse M.	104	98	98	100	104	96	90	90	98	94	104	96	80	98	100	94	96	100	104	92	100	98	100	104	100	98	88
Pulse E.	110	108	98	98	104	100	100	100	108	116	100	96	100	108	120	100	100	120	120	120	120	114	124	114	120	100	102
Resp. M.	26	26	24	26	24	24	24	24	24	22	26	24	24	26	24	24	26	24	28	24	24	26	28	24	28	24	24
Resp. E.	28	26	26	26	26	26	26	24	28	26	26	26	26	26	28	26	26	28	28	28	26	28	28	26	28	28	26
Stools.	1	3	3	2	2	1	1	0	0	2	1	1	0	1	2	1	1	1	2	1	3	3	3	1	2	1	1
Quantity	25	19	27	30	32	23	34	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·
Sp. Gr.	·	·	·	·	·	·	1029	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·
Albumen	·	·	·	·	·	·	0	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·
Sugar.	·	·	·	·	·	·	0	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·
Weight.			7st. 8lbs							7st. 8lbs.							7st. 12 lbs							8 st.			

urine

February. March.

Day of Month	21	22	23	24	25	26	27	28	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Pulse M.	90	92	86	84	90	92	88	80	84	96	104	94	92	90	82	80	80	90	86	88	70	70	72	86	70	70	66
Pulse E.	92	96	90	98	100	100	90	84	84	100	92	98	96	88	98	98	100	102	90	78	92	88	70	72	76	88	72
Resp. M.	26	26	26	24	24	26	20	26	22	24	28	22	24	22	20	20	24	20	18	22	20	18	16	20	20	18	16
Resp. E.	26	24	26	24	24	24	22	26	22	26	28	22	26	22	24	18	22	24	20	26	22	24	20	18	20	20	20
Stools.	1	1	1	0	2	3	1	2	3	1	0	0	4	1	4	3	1	2	1	0	1	1	1	2	3	1	2
Quantity.											•																
Sp. gr.											1020																
Albumen											O																
Sugar.											O																
Weight.				7st. 12 lbs.							8st.							7st. 13 lbs							8st 1 lb.		

Urine.

March. April.

Day of Month	20	21	22	23	24	25	26	27	28	29	30	31	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Pulse M	70	80	62	68	70	68	60	60	64	66	60	64	70	72	68	60	62	64	70	62	62						
Pulse E.	72	76	76	78	72	80	62	70	70	72	72	68	78	76	•	•	•	•	•	•	•						
Resp. M.	24	24	18	16	18	20	20	18	22	16	16	20	18	18	16	18	22	20	18	18	20						
Resp. E	24	20	20	18	22	18	18	20	24	20	20	24	22	26	•	•	•	•	•	•	•						
Stools.	0	1	2	1	1	1	2	1	1	2	1	2	2	2	1	3	0	0	1	2	1						
Quantity.																											
Sp. Gr.																											
Albumen.																											
Sugar.																											
Weight.				8st. 3 lbs.							8st. 3 lbs.								8st. 6 lbs.								

Discharged.

Urine

CASE III.

Florence B. aet. 2I Domestic servant.

Admitted to the East Suffolk Hospital December 4th I896 complaining of palpitation, pain over the heart and of constant fainting. The present illness commenced about one year ago, but she has been worse for the last six months.

Her father and mother are alive,aged 42 and 4I years, she has seven sisters; there is no marked hereditary tendency traceable.

Her surroundings have not been very healthy,and food has sometimes been scarce. As a child she had measles, and two years ago she suffered from very severe diarrhoea, with occasional recurring attacks ever since.

On admission she weighed 7 st. I2 lbs, the development was fair but she was extremely pale, the exopthalmos was well marked. The temperature was normal. The lips and gums were colourless, the teeth were good, the tongue furred and red at the edges. The appetite was poor, and she had discomfort after food. She had suffered from thirst for the last six months.

There was no enlargement of the lymphatic glands. The Thyroid shewed a uniform fulness, both lobes and

the isthmus being affected. Though quite distinct, the enlargement was not excessive, the circumference of the neck being twelve and-a-half inches.

Examination of the blood shewed that the red blood corpuscles were reduced to 2,500,000 per cubic ~~centi~~-millimetre, and the hoemoglobin to 45 per cent.

The respiratory system shewed no abnormality.

Dyspnoea and palpitation were very troublesome on the slightest exertion. The Apex beat was in the fifth interspace, there was no increase in the cardiac dulness, blowing systolic murmurs could be heard at the apex and at the base of the heart, and also over the vessels of the neck and Thyroid, and a venous hum over the Jugular veins.

The pulse was 100 to 120 per minute, regular, and of low tension.

As in the last case Oliver's arteriometer shewed loss of arterial tone by the reversed measurement of the radial calibre. The average of several measurements shewing the radial calibre to be 1·0 millimetres in the sitting posture, and 1·6 millimetres when recumbent.

The patient perspired freely, and there was some oedema of the legs and ankles.

The urine was acid, sp. gr. 1024. no albumen, no sugar, and averaged from 35 to 45 ounces per diem.

The catamenia which had been scanty during the last year, had ceased during the last three or four months.

The pupils were slightly dilated, exopthalmos was uniform and well marked, Von Groefe's sign was present in both eyes.

The muscular tremor though present was not so well marked as in the last case. The reflexes, deep and superficial were unaltered. Vaso-motor paresis was present and a tâche cerebrale could easily be obtained.

On admission the patient was treated exactly the same as the last-reported case, except that at first tabellae of the Thymus extract were used, and subsequently the Elixir.

January 3rd. The patient's condition had improved but not to any great extent. She was still very anaemic. The exopthalmos was undoubtedly somewhat better; the Thyroid enlargement remained the same, but the vaso-motor tone had been restored. A tâche cerebrale could less easily be obtained, and the radial calibre was I·8 millimetres, both when the patient was sitting and recumbent.

The pulse-rate was reduced from 90 to 75 per minute.

January 31st. The improvement during the month had been more marked. The exopthalmos was better but still present, the Thyroid gland slightly diminished, the circumference of the neck now being eleven and three-quarter inches. The pulse-rate was 65 to 75 per minute, the catamenia had re-commenced, and the hoemic murmurs were now less audible.

The patient was now given Sulphate of Iron as well as the Thymus treatment. She weighed 8stone 7lbs, having increased 9 lbs in weight since her admission.

February 10th. Patient was discharged, her general health was much improved. The pulse-rate was 70 per minute, she now weighed 8st. 8lbs. The exopthalmos though improved was still present. The improvement in the exopthalmos not having been so marked as in the last-reported case.

The two other cases with whom I have tried Thymus treatment were out-patients, and consequently could not be watched in the same way. One case shewed no improvement, and the other commenced to improve, and then stopped attending the Hospital.

CASE NO IV.

Mrs B. aet.30, married.

Ten years ago she first noticed swelling of the Thyroid and at that time suffered very much from palpitation; she happened to be at Boston and was advised to have the Thyroid removed.

Six years ago she first noticed prominence of the eye-balls. The patient states that the swelling was at first more marked on the right side, and that subsequently the enlargement became uniform.

The prominence of the eye-balls was at first the same in both eyes.

I first saw Mrs B. with Mr Eades of Ipswich in October 1895. The exopthalmos was well marked and the same in both eyes, both lobes of the Thyroid were equally enlarged. Tachycardia, at this time was very troublesome. She wished at the time to marry, but had been advised not to do so; Mr Eades however, considered her condition might improve with marriage, as it did.

I saw the patient fourteen months after my first having seen her. She had very much improved and was now a good colour, The tachycardia was much better but the exopthalmos had only improved in the right eye, the left eye being still very prominent and the

upper lid retracted; and with this the Thyroid shewed a distinct enlargement on the left side only; the right lobe and the isthmus now feeling normal in size. Both pupils were widely dilated.

Referring to the four cases reported:-

The first case is one which might be brought forward as supporting a primary central nervous derangement as causing the symptoms of Graves disease; early polyuria and exopthalmos existing some time before any change could be detected in the Thyroid gland,[1] the symptoms becoming much worse as soon as Thyroid enlargement occurred.

The improvement following on the mental relief afforded by the partial restoration of her sight was also remarkable.

The existence of unilateral cases has been frequently pointed out; more marked enlargement of one lobe of the Thyroid and greater exopthalmos on the same side being of common occurrence, as was present in cases I and 2.

1. It is however possible for there to be a considerable amount of Thyroid enlargement without its detection by manipulation, as pointed out by Greenfield. I have seen a case where a cyst in the Thyroid was only just perceptible when the patient was in the erect posture, and yet nearly an ounce of fluid was withdrawn by aspiration.

The greater enlargement of the Thyroid and the more marked exopthalmos on one side is usually noticeable early in the disease and remains constant during its course; but as shewn in Case 4, a fact I have not seen recorded elsewhere, the Thyroid enlargement and exopthalmos may be symmetrical at first,and subsequently the Thyroidal enlargement and the exopthalmos may disappear or improve on one side, remaining in statu quo on the other side.

These unilateral changes must point to some central nervous derangement other than that caused by the circulation in the system of a toxic agency which might reasonably be expected to affect both sides alike.

The toxic influence of the Thyroid secretion is undoubtedly a most important factor in the disease, and I considered that many of the wide-spread changes in the nervous system and some of the symptoms, e.g. the wasting, diarrhoea,sickness etc. are entirely due to this agency. And that the primary disturbances in the central nervous system,leading to the changes occurring in the Thyroid and the earlier exopthalmos are greatly augmented as soon as the Thyroid secretion, probably perverted, is super-added.

Referring to Cases 2 and 3:-

It has been suggested that the Thymus gland may have a controlling effect over the Thyroid and vice-versa. That Thymus secretion has the power of counter-acting results due to Thyroid secretion is I think undoubted, although the Thymus secretion is less active than the Thyroid and requires, when used medicinally,to be given in large amounts to give satisfactory results.

I consider that Thymus treatment is more likely to be successful in less acute cases of Graves disease, when the Thyroid secretion is probably less active.

Case 2 was very much benefitted by Thymus treatment. The patient had been ill six years,and during all that time had been constantly suffering.

Case 3 was a more acute one,and did not derive the same amount of benefit although her condition was much improved.

I am of the opinion that the improvement in Graves disease due to Thymus treatment, is greatly due to the counteracting of the vaso-motor paresis,and the restoration of the vascular tone. The rapid disappear-ence of a tâche cerebrale,and the appearence of the catamenia,as in casesII and III, support this supposition.

Measuring the radial calibre with Oliver's arteriometer, I have found that the normal measurements are 2 to 2·2 millimetres in the sitting posture, and I·6 to I·8 in the recumbent posture. Whereas in anæmia and Graves disease, in cases where the anæmia is not marked, this radial measurement is reversed as shewn in cases II and III. Further, that this radial measurement is restored to the normal under Thymus treatment.